Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment

Ying Wang[1–3] *and Rinaldo Bellomo*[1,4,5]

Abstract | Cardiac surgery-associated acute kidney injury (CSA-AKI) is the most common clinically important complication in adult patients undergoing open heart surgery, and is associated with increased mortality and morbidity. In patients in intensive care units, CSA-AKI is the second most common type of AKI after septic AKI. In this Review, we explore the definition of CSA-AKI, discuss its epidemiology and identify its risk factors. We discuss current theories of the pathophysiology of CSA-AKI and describe its clinical course. Furthermore, we introduce diagnostic tools with particular reference to novel biomarkers of AKI and their potential utility; we analyse currently applied interventions aimed at attenuating AKI in patients undergoing cardiac surgery; and describe evidence from randomized controlled trials aimed at preventing or treating CSA-AKI. Finally, we explore issues in the use of renal replacement therapy, its timing, its intensity and its preferred modalities in patients with CSA-AKI, and we discuss the prognosis of CSA-AKI in terms of patient survival and kidney recovery.

Acute kidney injury (AKI) is the most common major complication of cardiac surgery[1]. Each year, more than 2 million cardiac surgeries are performed worldwide[2] and the incidence of cardiac surgery-associated AKI (CSA-AKI) varies from 5% to 42%[3]. CSA-AKI is the second most common cause of AKI in the intensive care setting (after sepsis) and is independently associated with increased morbidity and mortality[4]. Severe CSA-AKI is independently associated with 3–8-fold higher perioperative mortality, prolonged length of stay in the intensive care unit (ICU) and in hospital, and increased cost of care[5]. The risk of death associated with AKI remains high for 10 years after cardiac surgery regardless of other risk factors, even for those patients with complete renal recovery[3].

CSA-AKI is a broad term that encompasses a range of pathologies. It can be classified as the type 1 form of cardiorenal syndrome (CRS), according to the CRS classification established in 2008 (REF. 6). CRS is a bidirectional condition that is defined as a pathophysiologic disorder of the heart and kidneys, whereby an abrupt deterioration of the function of one organ might induce acute or chronic dysfunction of the other organ[6]. Type 1 CRS reflects an abrupt worsening of cardiac function, which causes AKI[6].

Despite this cardiorenal theoretical framework, no consensus exists on the definition of CSA-AKI in the current literature. Over 35 different definitions of CSA-AKI, based on different diagnostic methodology, have been reported[7]. Most researchers have used the Acute Kidney Injury Network (AKIN) and/or the Risk, Injury, Failure, Loss, End Stage Kidney Disease (RIFLE) criteria to define AKI. These criteria are based on serum creatinine levels or a change in serum creatinine (increased by at least 1.5 times baseline) and urine output (<0.5 ml/kg/h for at least 6 hours)[8]. Unfortunately, in patients who have undergone cardiac surgery, these criteria are problematic because fluid resuscitation is common and fluid loading from the pump priming step during cardiopulmonary bypass (CPB) is universal. Thus, the application of AKIN and RIFLE criteria following cardiac surgery without correcting for serum creatinine changes owing to fluid balance leads to AKI being underdiagnosed[9]. Furthermore, the RIFLE criteria classify all patients who have undergone renal replacement therapy (RRT) as being in the 'failure' stage, but the criteria used to initiate RRT are not standardized[9].

The Kidney Disease: Improving Global Outcomes (KDIGO) criteria for AKI staging[10] demonstrate greater sensitivity to detect AKI and to predict associated in-hospital mortality, than do the RIFLE or AKIN criteria[11]. These criteria, which essentially merge the RIFLE and AKIN criteria, have become the new consensus

[1]*The Renal and Metabolic Division, The George Institute for Global Health, Level 5, 1 King Street, Newtown, New South Wales 2042, Australia.*
[2]*Concord Clinical School, The University of Sydney, New South Wales 2139, Australia.*
[3]*The Sydney Adventist Hospital, Wahroonga, Sydney, New South Wales 2076, Australia.*
[4]*Intensive Care Unit, The Royal Melbourne Hospital, Parkville, Melbourne, Victoria 3050, Australia.*
[5]*School of Medicine, University of Melbourne, Parkville, Melbourne, Victoria 3010, Australia.*

Correspondence to R.B.
rinaldo.bellomo@austin.org.au

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Key points

- CSA-AKI is the second most common cause of AKI in the intensive care setting and is associated with increased mortality
- The pathophysiology of CSA-AKI is very complex and probably includes renal ischaemia–reperfusion injury, inflammation, oxidative stress, haemolysis and nephrotoxins
- To date, no consensus definition for CSA-AKI exists, but the KDIGO criteria for AKI are commonly used in clinical practice
- To date, no pharmacological or non-pharmacological preventive strategies have been shown to reduce the occurrence of CSA-AKI in clinical trials
- The management of CSA-AKI requires a multifaceted approach
- Renal replacement therapy is necessary in 1–5% of patients with CSA-AKI and is associated with poor patient and renal prognosis, both in the short and long-term

definition of AKI and can be used to diagnose CSA-AKI (BOX 1). Any patient who has had cardiac surgery in the past week and fulfils the KDIGO criteria for AKI can be said to have CSA-AKI. Nevertheless, to date, the use of KDIGO criteria in these patients has been limited. Furthermore, in addition to clinical criteria, some researchers have proposed the use of novel biomarkers, such as urinary α1 microglobulin, *N*-acetyl-β-D-glucosaminidase, glutathione transferase-π, serum and urinary neutrophil gelatinase-associated lipocalin (NGAL), to aid in the identification of CSA-AKI[12]. Some urinary biomarkers (for example, IL-18 and kidney injury molecule 1 (KIM1)) seem to not only predict the development of subclinical AKI, which is characterized by an elevation in urinary biomarkers in the absence of rising serum creatinine levels, but also to have a prognostic value in terms of mortality 3 years after cardiac surgery[13]. However, the validity and applicability of biomarkers to a broad population of patients who have undergone cardiac surgery remain untested.

Box 1 | **KDIGO criteria for the diagnosis of CSA-AKI**

The Kidney Disease: Improving Global Outcomes (KDIGO) criteria[10] can be used to diagnose and stage cardiac surgery-associated acute kidney injury (CSA-AKI).

Definition of AKI

- An increase in serum creatinine by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 h.
- An increase in serum creatinine to ≥1.5–1.9 times baseline levels, which is known or presumed to have occurred within the prior 7 days.
- Urine volume <0.5 ml/kg/h for 6 h.

Staging of AKI

Stage	Serum creatinine	Urine output
1	Increase in serum creatinine by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 h from the onset of the disease or after cardiac surgery, or increase in serum creatinine of 1.5–1.9-fold of the baseline level	<0.5 ml/kg/h for 6–12 h
2	Increase in serum creatinine of 2.0–2.9-fold of the baseline level	<0.5 ml/kg/h for ≥12 h
3	Increase in serum creatinine of 3.0-fold of the baseline level or increase in serum creatinine to ≥4.0 mg/dl (≥353.6 μmol/l) or initiation of renal replacement therapy	<0.3 ml/kg/h for ≥24 h or anuria for ≥12 h

In summary, the KDIGO criteria represent the current epidemiologic and clinical standard for diagnosing acute kidney injury, including CSA-AKI.

In this Review, we discuss the epidemiology, pathophysiology, risk factors, diagnosis, prevention and management of CSA-AKI. We focus on the early phase of CSA-AKI, which occurs within the first 7 days after cardiac surgery. The late phase, which occurs between 7 days and 30 days after cardiac surgery, is not fully understood and is probably heterogeneous, and therefore is not discussed.

Epidemiology and clinical course of CSA-AKI

Over the last two decades, a lack of consensus on the definition of CSA-AKI has led to various incidences being reported[14,15]. Furthermore, owing to differences in baseline characteristics and in surgery type, reported incidences continue to vary between studies despite the publication of the KDIGO criteria[10]. Thus, the range of incidence reported based on KDIGO criteria varies between 3.1% and 42% according to the population of interest[3,16]. A large clinical epidemiological study of more than 50,000 adult patients undergoing a range of major in-patient surgeries in a single centre found that 39% of patients developed postoperative AKI defined using RIFLE criteria[17]. In this study, postoperative AKI was associated with a prolonged hospital stay, more postoperative complications and an increased cost of care[17]. Furthermore, patients with AKI had a 1.48-fold increase in mortality at postoperative day 90 (REF. 17) and increased cardiovascular mortality at 10-year follow-up[18] compared with those who did not develop postoperative AKI.

CSA-AKI can be divided into two phases, the early and the late phase, based on the timing of AKI occurrence. CSA-AKI can present as acute or chronic CSA-AKI and as AKI occuring before cardiac surgery or AKI occurring after cardiac surgery. The diagnosis of AKI and chronic kidney disease (CKD) before cardiac surgery should be based upon a serum creatinine level that has been obtained within a 3-month period preceding cardiac surgery. The clinical course of CSA-AKI can be extremely varied and is closely related to the overall health of the patient. In patients with postoperative cardiogenic shock that requires advanced haemodynamic support, AKI can be severe and can persist for weeks or even months. In other patients who show rapid overall recovery, the increase in serum creatinine levels can be short-lived (2–3 days) and can quickly decrease to normal levels.

Theories of CSA-AKI pathophysiology

The pathophysiology of AKI following cardiac surgery remains incompletely understood, is complex and probably involves multiple factors that operate in different ways and to differing extents in different patients (FIG. 1). Several major injury pathways are probably involved in the development of CSA-AKI, including hypoperfusion, ischaemia–reperfusion injury, neurohumoral activation, inflammation, oxidative stress, nephrotoxins and mechanical factors. All of these

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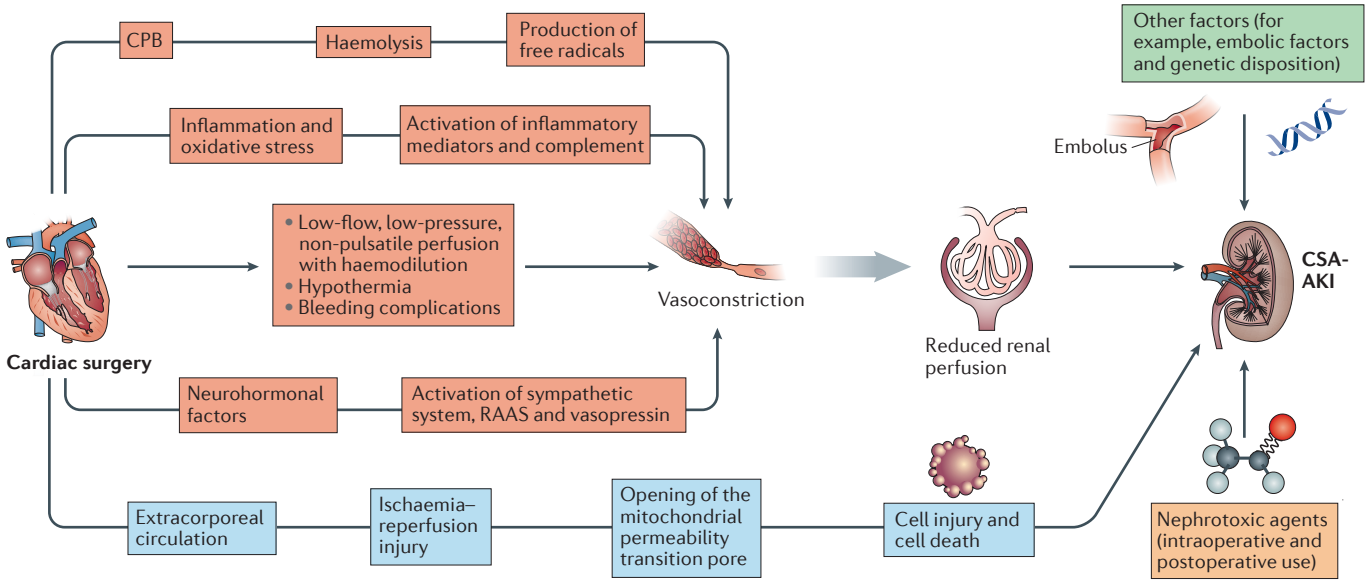

Figure 1 | **Potential pathophysiological pathways in CSA-AKI.** Cardiac surgery-associated acute kidney injury (CSA-AKI) can be caused by reduced renal perfusion that results from vasoconstriction after cardiac surgery. A number of pathophysiological pathways can lead to vasoconstriction (red boxes). CSA-AKI can also be caused by ischaemia–reperfusion injury that occurs in the extracorporeal circulation (blue boxes), leading to the opening of mitochondrial permeability transition pores in the kidneys and to cell injury or cell death. In addition, nephrotoxic agents (orange box) and other factors (green box) can contribute to CSA-AKI. CPB, cardiopulmonary bypass; RAAS, renin–angiotensin–aldosterone system.

injury pathways can occur preoperatively, intraoperatively and postoperatively[19], or at all of these times, and to varying degrees in any given patient.

Renal hypoperfusion after CSA-AKI

Cardiac surgery is often associated with renal hypoperfusion, resulting from the low-flow, low-pressure, non-pulsatile perfusion with haemodilution and rapid temperature changes that are associated with CPB. Bleeding complications as well as an inflammatory response may contribute to renal hypoperfusion. In addition to the CPB-induced changes in haemodynamics, a low cardiac output is a common trigger for AKI in the early postoperative period[20,21]. If a low cardiac output state or a hypotensive state persists, renal impairment will occur, probably owing to continued hypoperfusion causing a fall in glomerular filtration rate (GFR). Prolonged renal ischaemia is likely to lead to structural tubular injury, with renal tubular epithelial cell disruption causing tubular dysfunction. This renal hypoperfusion and tubular cell injury occurs when oxidant injury and inflammatory events are also present[22].

After CPB, renal perfusion may improve. However, ischaemia–reperfusion injury (IRI) may then occur and may contribute to AKI by leading to the opening of mitochondrial permeability transition pores (mPTPs) in the kidneys, which is associated with cell injury or cell death[23,24]. Another injury pathway in AKI that is caused by IRI is the production of reactive oxygen species (ROS)[25], which further induces inflammation by upregulating pro-inflammatory transcription factors, including nuclear factor-κB[26]. Cytokines and chemokines activate neutrophils, macrophages, and lymphocytes and recruit them into the renal parenchyma, causing parenchymal infiltration and thus contributing to AKI[27].

The development of intravascular haemolysis is associated with the use of CPB and is characterized by an acute rise in free haemoglobin[28]. Free haemoglobin potentially causes tubular epithelial cell injury, possibly via increased intravascular nitric oxide consumption that limits its bioavailability, which leads to decreasing renal perfusion[29]. Free haemoglobin also induces haem oxygenase 1 (HO1) expression and may contribute to CSA-AKI by direct toxicity[30].

Inflammation and oxidative stress

Surgical injury to tissues and the exposure of blood to the CPB pump and circuit is associated with the activation of multiple inflammatory pathways, and increases in the levels of pro-inflammatory cytokines compared with operations done off-pump are observed[31]. Complement activation via the alternative complement pathway during exposure to CPB may also contribute to development of AKI after cardiac surgery[31]. In support of this idea, an increase in plasma concentrations of inflammatory cytokines postoperatively is associated with a subsequent diagnosis of AKI and with increased mortality[32].

CPB also causes oxidative stress, which may be an important mechanism in the development of CSA-AKI[33]. The production of free radicals and the release of catalytic iron during haemolysis following CPB are associated with myocardial injury and AKI in a number of animal studies[34]. Oxido-inflammatory stress may also be exacerbated by IRI during CPB[35], causing increased free circulating labile iron. Labile catalytic iron can induce multiple changes in renal tubular epithelial cells, such

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as impaired cell proliferation and the induction of lipid peroxidation and protein oxidation[36].

Nephrotoxins, mechanics and genetics

Patients undergoing cardiac surgery are usually exposed to nephrotoxic agents, such as antibiotics (for example, glycopeptides and aminoglycosides) and non-steroidal anti-inflammatory agents, both before and after procedures. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) can cause volume depletion and renal efferent arteriolar vasodilation, respectively, and can contribute to AKI[37].

Neurohormonal adaptations can occur in cardiac surgery and are often triggered by haemodynamic changes. These adaptations may activate the sympathetic nervous system and the renin–angiotensin–aldosterone system, and may increase the production of vasopressin and endothelin 1, leading to systemic vasoconstriction and subsequent reduced renal perfusion[38].

Septic embolism occurs in ~30% of patients with infective endocarditis undergoing cardiac valve replacement, and can lead to renal infarction, renal cortical necrosis and immune complex-mediated glomerulonephritis[39].

Cholesterol embolization can occur during and after cardiac surgery, especially in patients with pre-existing atherosclerosis[40]. It causes AKI secondary to occlusion of renal artery branches, arterioles and glomerular capillaries by atheromatous plaques that are dislodged from the aorta and other major arteries, and that trigger complement activation[40].

Box 2 | **Risk factors for CSA-AKI**

Risk factors for cardiac surgery-associated acute kidney injury (CSA-AKI) are classified as patient-related or procedure-related factors, as well as by the relevance of the risk factors at different times with respect to the cardiac surgery procedure.

Patient-related factors

Female sex; advanced age; chronic obstructive pulmonary disease (COPD); diabetes mellitus; peripheral vascular disease; pre-existing chronic kidney disease; congestive heart failure; left ventricular ejection fraction <35%; need for emergency surgery; cardiogenic shock (requiring intra-aortic balloon pump (IABP)); left main coronary artery disease; previous cardiac surgery.

Procedure-related factors

Cardiopulmonary bypass (CPB) time; cross-clamp time; on-pump versus off-pump; haemolysis; haemodilution; pulsatile versus non-pulsatile perfusion.

Preoperative factors

Advanced age; female sex; renal dysfunction; heart failure; left main coronary artery disease; diabetes mellitus; COPD; peripheral vascular disease; liver disease; low cardiac output states or hypotension (cardiogenic shock from acute myocardial infarction, mechanical complications of myocardial infarction); nephrotoxins.

Intraoperative factors

Type of surgery (valvular, valvular and coronary, emergency and redo surgery); CPB non-pulsatile, low-flow, low-pressure perfusion; hypothermic CPB; deep hypothermic circulatory arrest; CPB duration >100–120 min; haemodilution; haemolysis and haemoglobinuria from prolonged duration of CPB; embolism.

Postoperative factors

Low cardiac output states (decreased contractility, hypovolaemia and absent atrioventricular synchrony in hypertrophied hearts); hypotension; intense vasoconstriction; atheroembolism (requiring IABP); sepsis; nephrotoxins.

A number of genetic polymorphism studies have demonstrated the role of genetic predisposition in the development of CSA-AKI. For example, the presence of apolipoprotein E (APOE), an important protein that is responsible for lipoprotein metabolism, tissue repair and immunomodulation, was protective and was associated with a lower peak serum creatinine level and a reduction in postoperative serum creatinine elevation in patients undergoing cardiac surgery[41,42]. A prospective study of 111 patients receiving coronary artery bypass grafting (CABG) demonstrated that the 174 G>C polymorphism in the *IL-6* gene correlated with higher postoperative plasma IL-6 levels and the development of AKI[43].

Although all of the above factors have been associated with CSA-AKI, the evidence supporting their role in CSA-AKI is associative rather than causal. Moreover, because of the huge logistic challenges and costs, animal models of cardiac surgery that include CPB and recovery have not been developed. Thus, our understanding of the pathophysiology of CSA-AKI remains rudimentary.

Risk factors and prediction of CSA-AKI

Most of the information on risk factors for CSA-AKI comes from retrospective observational studies (BOX 2). These risk factors can be classified as preoperative, intraoperative and postoperative.

Risk factors for CSA-AKI

Common preoperative risk factors for the development of CSA-AKI include female sex, advanced age, the presence of multiple comorbidities (for example, pre-existing CKD, previous cardiac surgery, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, hypercholesterolaemia, congestive heart failure and a left ventricular ejection fraction of <35%) and obesity[44].

Patients with intraoperative exposure to nephrotoxic agents (such as contrast media or aminoglycoside antibiotics) and those who undergo emergency surgery are also susceptible to CSA-AKI[45]. The type of cardiac surgical procedure also has a marked impact on renal outcomes[46]. For example, complex cardiac surgery (such as valve replacement, valve repair, combined valve and coronary surgery, redo surgery and aortic arch surgery) is associated with a substantially higher risk of postoperative AKI and a greater incidence of severe AKI requiring dialysis than is less complex surgery[47].

CPB itself may be associated with an increased risk of CSA-AKI, suggesting that exposure to an extracorporeal circuit is a factor in the development of AKI[48]. A systematic review of 33 randomized controlled trials (RCTs) that included 1,732 patients undergoing cardiac surgery, suggested that, compared with on-pump CABG, off-pump CABG might be associated with reduced risk of AKI (RR 0.87, 95% CI 0.77–0.98)[49]. However, this finding was based on data from small trials. Two large RCTs (the CORONARY and ROOBY studies) did not fully support the proposed renoprotective effects of off-pump surgery. In the CORONARY study[50,51], 4,752 patients were randomly assigned to either on-pump or off-pump CABG. No significant differences were reported between patients undergoing off-pump and on-pump CABG in 30-day

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and one-year mortality, or in the incidence of myocardial infarction or stroke. The use of off-pump CABG resulted in a decreased incidence of transfusion, reoperation for perioperative bleeding, respiratory complications and AKI, but did not affect the number of patients with AKI requiring dialysis. Furthermore, off-pump CABG resulted in an increased risk of early revascularization compared with on-pump CABG.

The ROOBY study[52], which included 2,203 patients undergoing CABG, did not show any survival benefits or renoprotective effects of off-pump compared with on-pump surgery. Off-pump surgery was associated with a higher rate of cardiac death and lower rate of graft patency at 1-year follow-up. The prospective randomized HEPCON trial[53] assessed renal outcomes in patients undergoing CABG who were treated with one of three surgical techniques, namely, conventional extracorporeal circulation (CECC), minimized extracorporeal circulation (MECC) and off-pump CABG. The results showed that CECC temporarily induced more tubular injury in the early post-CABG period than did MECC or off-pump CABG. Other reported procedure-related risk factors, such as prolonged duration of CPB, prolonged aortic cross-clamping, non-pulsatile flow of CPB, haemolysis and haemodilution, may increase the risk of AKI[54]. On aggregate, these findings suggest that the renal impact of CPB *per se* is limited.

Exposure to nephrotoxins, postoperative development of cardiogenic shock, low haematocrit levels (<24%)[55,56], and transfusion of more than two units of blood[57] have also been reported to be associated with a high risk of CSA-AKI.

Among the risk factors discussed above, preoperative risk factors are patient-related and tend to be non-modifiable, whereas adjusting intraoperative and postoperative risk factors, such as the procedure itself, exposure to nephrotoxic agents, and whether or not blood transfusion is given, might reduce the incidence of AKI[58].

Predicting CSA-AKI

Early identification of patients at high risk of CSA-AKI using risk prediction models enables clinicians to closely monitor these patients and to initiate efficient preventive and therapeutic strategies to reduce the incidence of AKI. Several risk prediction models for AKI have been developed, but no guidelines exist to recommend the use of a specific prediction model for CSA-AKI. The Cleveland Clinic Score[59], the Mehta Score[60], and the Simplified Renal Index (SRI) score[61] are validated for predicting severe AKI that requires dialysis. The first model for predicting all stages of AKI was developed using KDIGO criteria in a prospective study of >30,000 patients[62]. This model showed improved discrimination compared with the Cleveland Clinic Score and equivalent discrimination to the Mehta score. In addition to clinical risk factors, the integration of novel biomarkers into prediction models might aid the early identification of patients at high risk. The TRIBE-AKI study demonstrated improvements in the prediction of CSA-AKI risk of 25% and 18% when using the biomarkers urine IL-18 and plasma NGAL, respectively, in addition to clinical risk factors[63].

Diagnosis and novel biomarkers

CSA-AKI is characterized by an abrupt deterioration in kidney function following cardiac surgery, which is evident from a reduction in GFR[4]. Under normal circumstances, the serum creatinine level increases by 0.1–0.2 mg/dl (8.8–17.7 μmol/l) following cardiac surgery. If the creatinine level increases by ≥0.3 mg/dl (26.5 μmol/l) within 48 h, the patient is considered to have stage 1 AKI according to the KDIGO criteria[64].

The use of serum and urinary biomarkers is an additional and promising new approach for the early diagnosis of CSA-AKI (BOX 1). However, the use of biomarkers remains more cumbersome than other diagnostic approaches and is not widely available. The serum creatinine level is traditionally used as a biomarker for renal impairment, but its usefulness can be affected not only by physiological processing (for example, urinary clearance of creatinine, or muscle mass) but also by drugs that block the tubular secretion of creatinine and by some underlying medical conditions, such as diabetes and liver disease[65].

Given the limitations of serum creatinine as a biomarker, there has been increasing interest in the last decade in the identification of new serum and urinary biomarkers for the early diagnosis and prognostication of AKI following cardiac surgery. New biomarkers could aid early diagnosis of AKI, even in the absence of concurrent renal dysfunction[66]. In response to ischaemic or nephrotoxic injury, tubular cell proteins are released into the urine. Thus, measurement of urinary biomarkers may be more specific and more sensitive than the measurement of serum biomarkers for the detection of AKI. Compared with urinary biomarkers, serum biomarkers are less specific, as they can be affected by other conditions and by cardiac surgery, rather than by kidney function alone. The EARLYARF trial was the first RCT to use a urinary biomarker-based approach to facilitate the early detection of AKI and so trigger erythropoietin treatment[67]. The product of the concentrations of two urinary biomarkers, γ-glutamyl transpeptidase (GGT) and alkaline phosphatase (AP), was selected for its diagnostic value. The product of the biomarker concentrations was associated with disease severity, an increased risk of AKI, a requirement for RRT, and mortality; however, elevation in the level of the markers was transient. Overall, these biomarkers showed poor predictive performance in these patients with a heterogeneous timing of onset of injury[67].

Other biomarkers that have been more commonly investigated for their potential role in the early detection of AKI (TABLE 1). Proteins such as NGAL, IL-18, KIM1, liver fatty acid-binding protein (L-FABP), cystatin C (CST3C), tissue inhibitor of metalloproteinases 2 (TIMP2) and insulin-like growth factor-binding protein 7 (IGFBP7), so-called cell cycle arrest biomarkers, have been investigated in animal models and in preliminary human studies, and are promising biomarkers of AKI[68]. For example, the level of urinary IGFBP7 and TIMP2, the two biomarkers that are involved in G1 cell cycle arrest[69], accurately predicted CSA-AKI[70]. In a RCT, an increase in the product of

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urinary [TIMP2] and [IGFBP7] occurred immediately after remote ischaemic preconditioning (RIPC) in high-risk patients undergoing cardiac surgery; the RIPC intervention was associated with a reduced incidence of AKI[71]. The investigators suggested that the product of urinary [TIMP2] and [IGFBP7] may have a renoprotective effect, which is consistent with a role in an epithelial defence mechanism via the induction of G1 cell cycle arrest[72].

Novel biomarkers seem to improve risk stratification of CSA-AKI. However, the superiority of one biomarker over another, and the superiority of biomarkers over clinical models, are uncertain. At this stage, the use of biomarkers should not replace thorough clinical assessment of patients with AKI. Finally, the cost-effectiveness of using novel AKI biomarkers in clinical practice remains unclear.

Management of patients with CSA-AKI

The management of patients with CSA-AKI requires a multifaceted approach that includes early diagnosis, monitoring of renal function, and preventive and therapeutic interventions.

Preventive and therapeutic interventions

The current key principles for the prevention of CSA-AKI are based on inductive physiological and pharmacological thinking. The conventional physiological assumption is that decreased oxygen delivery to the kidney because of low cardiac output, low mean arterial pressure, or both, is the major mechanism of injury in patients undergoing cardiac surgery. Accordingly, clinicians seek to avoid a low cardiac output by the use of judicious plasma volume expansion and inotropic drug administration.

Simultaneously, clinicians also seek to avoid a hypotensive state by the judicious use of intravenous fluids and vasopressor drugs. These therapies are dynamic and are guided by multiple signals obtained by invasive means (such as cardiac output, mean arterial pressure, cardiac filling pressures, stroke volume variation, pulse pressure variation, mixed venous oxygen saturation, and transoesophageal and/or transthoracic echocardiography (the latter is difficult after cardiac surgery)). The decisions of clinicians are also informed by additional information, such as physical examinations (for example, measurements of peripheral temperature and capillary return time), blood lactate levels, urinary output and serum haemoglobin and creatinine concentrations. The interpretation of all of this information, the choice of haemodynamic targets, the interventions applied to patients with CSA-AKI at any moment in time, and the assessment of response to therapy, all remain an art rather than a science. This approach is used because of the extraordinary complexity and moment-to-moment or patient-to-patient differences in CSA-AKI. As such, the additional parameters listed above have not been investigated in RCTs. However, a RCT of angiotensin II for the treatment of vasodilatory shock[73], which included patients with post-CPB vasoplegia, reported a beneficial effect of this therapy on blood pressure control as well as an 8% absolute reduction in mortality risk[74].

Pharmacological inductive thinking is simpler and focuses on avoiding, whenever possible, the use of potentially nephrotoxic drugs (such as non-steroidal anti-inflammatory agents, aminoglycoside antibiotics, radiocontrast agents, ACE inhibitors and ARBs) around the time of cardiac surgery.

Beyond these principles of management, there is a lack of robust and reproducible level 1 evidence from RCTs for the efficacy of other interventions in the prevention of CSA-AKI. For example, no known pharmacological and non-pharmacological preventive strategies have been shown in large phase III clinical trials to reduce the occurrence of CSA-AKI[75,76], although some treatments may be effective in specific patient populations[71].

Given these challenges, the KDIGO guidelines recommend the following general strategies to reduce AKI: discontinuation of nephrotoxic agents, optimization of blood glycaemic control, close monitoring of serum creatinine level and urine output, as well as maintenance of haemodynamic stability[10]. To support these KDIGO guidelines, discontinuation of nephrotoxic agents was investigated in a systematic review of six studies with 1,663 total participants, including three RCTs and three prospective cohort studies[77]. Five of these studies evaluated the discontinuation of nephrotoxic agents before coronary angiography and one evaluated discontinuation before cardiac surgery. The discontinuation of ACE inhibitors and ARBs was investigated in five studies, whereas one small cohort study looked at the discontinuation of nonsteroidal anti-inflammatory drugs. Overall, the continuation of nephrotoxic agents was associated with an approximately 15% increased risk of AKI compared with discontinuation (RR 1.17, 95% CI 0.99–1.38); however, this difference was not statistically significant.

Strategies for prevention of CSA-AKI

Statins. Long-term statin therapy is common in patients who have undergone cardiac surgery[78]. In observational studies, perioperative statin therapy seems to be associated with a decreased level of C-reactive protein, a lower incidence of atrial fibrillation and a shorter length of hospital stay compared with patients not taking statin therapy[79–81]. Animal studies have shown that statins have pleiotropic effects and can ameliorate endothelial dysfunction, inhibit oxidative pathways, increase nitric oxide bioavailability and reduce inflammatory responses[82], which further supports a protective role in CSA-AKI. A retrospective study demonstrated a prophylactic effect of the perioperative use of statins for postoperative AKI[83], and early postoperative statin use seemed to be associated with a lower incidence of AKI[84,85]. However, a number of large RCTs have found that the use of statins does not reduce postoperative AKI or hospital mortality in the setting of cardiac surgery[76,86–89].

Remote ischaemic preconditioning. RIPC is elicited by brief episodes of ischaemia and reperfusion in distal tissues, which might provide protection from subsequent injury[90]. RIPC has been advocated as a means of mitigating AKI after cardiac surgery, as it can release

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various molecules, such as damage-associated molecular patterns, which are filtered by the kidney and can activate Toll-like receptors in the proximal tubule epithelia[90,91]. Activation of Toll-like receptors can induce natural defences[92], such as bioenergetic downregulation and temporary cell cycle arrest, and further protect the kidney during subsequent stress.

RCTs have demonstrated variable effects of RIPC on CSA-AKI[75,93–95] (Supplementary information S1 (table)). To summarize the 2017 Cochrane review, an analysis of the effect of RIPC in 28 RCTs of 6,851 patients undergoing surgical interventions associated with renal ischaemia and reperfusion concluded that RIPC led to little or no difference in serum creatinine levels, the incidence of

Table 1 | **Novel biomarkers in CSA-AKI**

Marker	Description	Advantages	Disadvantages	Examples of studies
NGAL	Serum and urinary marker of tubular damage[168,169]	• Levels increase rapidly after renal ischaemia–reperfusion injury • High diagnostic value in CSA-AKI, especially in patients with normal renal function at baseline	• Changes in NGAL levels are not restricted to AKI, but can also be affected by age, anaemia, cancer, CKD and inflammatory conditions • NGAL has a possible renoprotective role in ischaemic injury	The TRIBE study showed that measurement of urinary and plasma NGAL concentrations improved prediction of CSA-AKI risk[170]
KIM1	Urinary marker of tubular damage	High sensitivity and specificity	Conflicting results from paediatric studies on the predictive value for AKI[171,172]	Moderately accurate predictive marker[171] or no predictive value for CSA-AKI[172]. Urinary KIM1 level was increased in children who developed AKI following CPB
Cystatin C	• Cysteine proteinase inhibitor • Serum and urinary marker of glomerular filtration	Levels are not affected by sex or muscle mass	Discordant results from studies on the predictive value of cystatin C for CSA-AKI (compared with serum creatinine)[173,174]	A prospective cohort study of 72 patients showed that urinary cystatin C is a predictive marker for AKI after cardiac surgery[174]
L-FABP	• Small cytoplasmic protein • Urinary marker of tubular damage	Urinary L-FABP levels predict poor outcomes, such as the requirement for RRT or the composite end point of death or RRT[179]	Urinary L-FABP levels can also be increased in CKD[180]	L-FABP levels moderately predict CSA-AKI[172]. Urinary L-FABP level was increased in children who developed AKI following CPB
IL-18	• Pro-inflammatory cytokine • Urinary marker of tubular damage	Levels increase after ischaemia–reperfusion injury[175]	IL-18 levels probably only rise in intrinsic AKI and not in prerenal AKI[176]	Early predictive marker for CSA-AKI[177,178]. A prospective study showed that urinary IL-18 level was increased in 20 patients who developed AKI after cardiac surgery
TIMP2 and IGFBP7	Urinary biomarkers of cell cycle arrest	Urinary measurement of the product of [TIMP2] and [IGFBP7] shows better diagnostic performance of AKI risk stratification than standard clinical assessment	TIMP2 can also promote cellular proliferation and is strongly expressed in renal cell carcinoma[181]	Product of [TIMP2] and [IGFBP7] was a predictor for AKI in a study including 51 children undergoing CPB[182]
ROBO4	• Transmembrane receptor expressed in endothelial cells • Marker for endothelial dysfunction	Levels increase transiently following cardiac surgery (whereas NGAL remains elevated at 24 h after surgery)	Expression is not restricted to the kidney (ROBO4 is also expressed in haematopoietic stem cells)[183]	Elevated ROBO4 was an early predictor for AKI after CPB in a study of 32 patients, which correlated with positive NGAL at 2 h after surgery[184]
Semaphorin 3A	Expressed in the developing glomerulus, podocytes and collecting ducts[185]	Early urinary semaphorin 3A level was associated with clinical outcomes (such as requirement for RRT, and hospital length of stay)[186]	Evidence requires validation in a larger study, as current data are from a small single-centre study only	A *post hoc* analysis showed that urinary semaphorin 3A predicted AKI at 2 h after CPB[186]
Netrin 1	Marker of tubular injury	In preclinical studies, appears in the urine early (within 1–3 h) after AKI and also correlates with duration and severity of AKI and length of hospital stay[187]	Netrin 1 levels can also be elevated in CKD	Early predictor for AKI after CPB (levels peaked at 6 h after CPB) in a study of 26 patients[187]

AKI, acute kidney injury; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; CSA-AKI, cardiac surgery-associated AKI; IGFBP7, insulin-like growth factor-binding protein 7; KIM1, kidney injury molecule 1; L-FABP, liver fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; ROBO4, roundabout guidance receptor 4; RRT, renal replacement therapy; TIMP2, tissue inhibitor of metalloproteinases 2.

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adverse effects, the need for dialysis, length of hospital stay, probability of death and the incidence of AKI[96].

Intravenous bicarbonate. Urinary alkalinization might have antioxidant properties and may reduce complement activation and prevent tubular haemoglobin cast formation and haemoglobin-induced pigment nephropathy, all of which might protect against renal injury[97]. Whether administering intravenous bicarbonate to induce urinary alkalinization prevents CSA-AKI remains uncertain, as published RCTs have given discordant results. An individual patient meta-analysis of three double-blind RCTs that included 877 patients concluded that sodium bicarbonate infusion was not associated with a lower overall incidence of AKI[98]. However, sodium bicarbonate infusion might reduce the incidence of severe AKI and the need for renal replacement therapy in patients undergoing elective coronary artery bypass.

Fenoldopam. Fenoldopam is a selective agonist of dopamine D_1 receptors that causes relaxation of smooth muscle, vasodilatation and inhibition of tubular reabsorption of sodium in the kidney. In healthy volunteers and in patients with hypertension, intravenous fenoldopam administration was associated with increased renal blood flow and decreased vascular resistance via its selective renal vasodilatatory and natriuretic effects[99]. Furthermore, in small studies, fenoldopam had a renoprotective effect in the setting of cardiac surgery when administered for at least 24 h starting from the initiation of CBP at rates of >0.1 mg/kg/min[100]. A systematic review and meta-analysis of six randomized placebo-controlled trials including 440 patients found that fenoldopam use was associated with a 59% reduction in the risk of AKI. However, all of these studies had small sample sizes and were of variable quality. A definitive, multicentre, randomized, double-blind, placebo-controlled, parallel-group study[101] failed to show any renoprotective effects or survival benefits of fenoldopam infusion in patients undergoing cardiac surgery. In fact, fenoldopam was associated with an increased rate of hypotension in this trial.

Mannitol. Mannitol is an osmotic diuretic that is widely used in the priming fluid for CPB to reduce the incidence of renal dysfunction. However, two small RCTs comparing mannitol with an equivalent volume of Hartmann's solution in the pump prime, in patients with either normal preoperative renal function or with serum creatinine levels of 130–250 umol/l, did not show any difference between these two groups in renal function, urine output, or in the levels of urinary retinol-binding protein and microalbuminuria during the early postoperative period[102,103]. Another study demonstrated that mannitol infusion increased urine flow, renal blood flow and the renal blood flow:cardiac output ratio, and decreased renal vascular resistance in the setting of CSA-AKI, but no evidence of changes in markers of GFR was observed[104]. Thus, the use of mannitol in the priming fluid for patients undergoing cardiac surgery cannot currently be recommended.

KDIGO-based approach to high-risk patients. The PrevAKI RCT is a single-centre trial to assess the effectiveness of implementing the KDIGO guidelines in the prevention of CSA-AKI in high-risk patients who were identified using biomarkers[105]. In this trial, the effect of a 'KDIGO bundle of care', which consists of optimization of volume status and haemodynamics, avoidance of nephrotoxic drugs and prevention of hyperglycaemia, in high-risk patients (defined as those with a product of urinary [TIMP2] and [IGFBP7] >0.3) undergoing cardiac surgery was examined. Compared with standard care, implementation of the 'KDIGO bundle of care' reduced the frequency and severity of AKI after cardiac surgery in high-risk patients. The mechanisms of these reductions might include improvement in renal perfusion[106] and decreases in inflammation[107] and oxidative stress[107]. Given these promising results, adequately powered multicentre trials are warranted to investigate the effect of the KDIGO approach on mortality and long-term renal outcomes, and to understand the role of biomarkers in the identification of patients who might benefit from specific interventions.

Fluid management and diuretics

Fluid management. Fluid management during and after cardiac surgery is complex and controversial. Concerns exist regarding excessive accumulation of extracellular fluid and intravascular hypovolaemia, both of which can contribute to AKI. In general, the cardiac index should be maintained at or near normal levels using invasive haemodynamically guided fluid therapy to attenuate renal hypoperfusion[108]. Such goals should be pursued together with seeking to minimize fluid overload and decreasing so-called maintenance fluid therapy[109].

Fluid overload in the setting of CSA-AKI can increase the risk of pulmonary oedema and organ congestion. An observational study showed that perioperative haemodynamic instability and fluid overload are associated with increased severity of AKI and increased mortality following cardiac surgery[110]. The type of fluid used may also matter. The SPLIT multicentre, double-blind, cluster-randomized, double-crossover trial in 2,278 patients who were admitted to the ICU requiring fluid therapy (approximately 50% of whom were having cardiothoracic surgery), demonstrated that use of a buffered crystalloid fluid did not reduce the risk of AKI compared with use of saline[111]. By contrast, a systematic review of 21 studies (15 RCTs) that included 6,253 patients, suggested that postoperative fluid resuscitation with balanced crystalloids was associated with a reduced incidence of CSA-AKI, compared with fluid resuscitation with physiologic saline solutions[112]. Another RCT reported a decrease in the incidence of hyperchloraemia with fluid resuscitation with a balanced crystalloid solution compared with saline[113]. A renoprotective effect of balanced crystalloids was not seen, however, in pooled analyses of data from RCTs only. Further large RCTs are therefore needed to assess the effects of different balanced fluid resuscitation methods on mortality and AKI in patients following cardiac surgery.

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Of note, large trials have shown that the use of hydroxyethyl starch (HES) for fluid resuscitation is associated with an increased risk of AKI[114]. Thus, the use of HES is contraindicated in patients at high risk of AKI undergoing cardiac surgery. Concerns regarding increased AKI risk have led to a major decrease in the use of HES in this setting[115].

Diuretics. The use of diuretics is common and they can be administered before and after cardiac surgery to reduce the risk of fluid overload. A small single-centre study suggested that prophylactic use of the diuretic furosemide might be associated with improved renal outcomes in cardiac surgery[116]. By contrast, a single-blinded RCT that included 123 patients did not show a beneficial effect of furosemide on renal function compared with placebo[117]. Furthermore, a double-blind RCT that included 126 patients with preoperatively normal renal function undergoing elective cardiac surgery showed a twofold increase in the incidence of postoperative acute renal injury in patients who were given furosemide during the procedure, as well as no renoprotective effect of dopamine[118]. These disappointing results reflect, in part, a limited understanding of the pharmacodynamics of intravenous furosemide in these patients[119].

Tolvaptan is a vasopressin V2 receptor antagonist that promotes an aquaretic effect. A small, multicentre, randomized, double-blind, placebo-controlled study that included 83 patients with heart failure and systolic dysfunction, found that tolvaptan monotherapy resulted in a reduction in body weight compared with furosemide therapy[120]. When tested in a small RCT of patients undergoing cardiac surgery[120], the combination of tolvaptan with conventional diuretics increased urine output without renal dysfunction.

Use of renal replacement therapy

The development of CSA-AKI leads to the initiation of RRT in 1–5% of cases[121]. Severe AKI that requires RRT is associated with especially poor outcomes[3]. The current literature on the use of RRT relates predominantly to patients in the ICU with severe AKI (TABLE 2). However, a substantial percentage of participants in the existing trials were treated after cardiac surgery. Furthermore, in the absence of data specific to cardiac surgery, clinicians deciding how to approach RRT in these patients will, inevitably, have to refer to general studies.

Timing of initiation of RRT. The ideal timing of RRT initiation after cardiac surgery remains uncertain. The KDIGO guidelines suggest that indications for initiating

Table 2 | **Randomized controlled trials of therapeutic interventions in CSA-AKI**

Trial	Multicentre (Yes/No)	Double blinded (Yes/No)	No. of patients		Intervention	Primary outcome data	Refs
			Total	Cardiac surgery			
RENAL (2009)	Yes	No	1,508	269 (17.8%)	Intensity of RRT	High-intensity continuous RRT did not reduce all-cause mortality at 90 days after surgery	127
ATN (2008)	Yes	No	1,124	463 (41.2%)	Intensity of RRT	No difference in mortality, rate of recovery of kidney function, duration of RRT and evolution of nonrenal organ failure between high-intensity and low-intensity RRT	126
AKIKI (2016)	Yes	No	620	126 (20.3%)	Timing of initiation of RRT	No difference in all-cause mortality between early and delayed initiation of RRT; 49% of patients in the delayed RRT group did not need RRT	124
ELAIN (2016)	No	No	231	108 (46.8%)	Timing of initiation of RRT	Early RRT initiation reduced mortality in the first 90 days after cardiac surgery	123
Kielstein *et al.* (2004)	No	No	39	NA	CVVH versus EDD	No significant difference in average mean arterial blood pressure, heart rate, cardiac output, systemic vascular resistance, urea reduction rate and catecholamine dose between interventions	130
CONVINT (2014)	No	No	252	13 (5.16%)	CVVH versus IHD	No survival difference after 30 days between CVVH and IHD group	188
Vinsonneau *et al.* (2006)	Yes	No	360	107 (29.7%)	CVVHDF versus IHD	No survival difference after 60 days between CVVHDF and IHD group	131
Badawy & Samir (2013)	No	No	80	80 (100%)	CVVHDF versus EDD	No significant difference in mortality and renal recovery between CVVHDF and EDD group; EDD seemed to be more cost-effective	133

CSA-AKI, cardiac surgery-associated acute kidney injury; CVVH, continuous venovenous haemofiltration; CVVHDF, continuous venovenous haemodiafiltration; EDD, extended daily dialysis; IHD, intermittent haemodialysis; NA, not available; RRT, renal replacement therapy.

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Table 3 | **Conventional criteria for initiation of renal replacement therapy in acute kidney injury**

Indications	Criteria
Clinical	• Anuria (negligible urine output for 6 h) • Severe oliguria (urine output <200 ml over 12 h) • Volume overload (especially pulmonary oedema that is unresponsive to diuretics) • Clinical complications of uraemia (for example, encephalopathy, pericarditis and neuropathy)
Laboratory	• Hyperkalaemia (potassium concentration >6.5 mmol/l) • Severe metabolic acidosis (pH <7.2 despite normal or low partial pressure of carbon dioxide in arterial blood) • Pronounced azotaemia (urea concentrations >30 mmol/l or creatinine concentrations >300 µmol/l)

RRT include the presence of life-threatening changes in fluid levels, electrolyte and acid–base balance[122]. The conventional indications for RRT initiation are summarized in TABLE 3. Two RCTs that investigated the effect of timing of initiation of RRT in general ICU patients with severe AKI were published in 2016 and had discordant results[123,124]. The AKIKI trial[124] is a multicentre RCT of 620 patients with KDIGO stage 3 AKI. No difference in mortality at day 90 following the randomization was seen between groups that received early initiation of RRT (within 6 h after documentation of stage 3 AKI) and delayed initiation of RRT (initiated if the patient developed uraemia with serum urea >40 mmol/l, hyperkalaemia with serum potassium >6.0 mmol/l or profound metabolic acidosis with pH<7.15 or if oliguria or anuria lasted for more than 72 h after randomization). Furthermore, almost 50% of patients in the delayed initiation group did not need RRT. The single-centre ELAIN trial showed a survival benefit of early RRT initiation compared with delayed initiation[123]. Although both the AKIKI and ELAIN trials included patients with severe AKI of different underlying aetiologies, approximately 50% of patients in the ELAIN trial received cardiac surgery. The findings of the ELAIN trial are, therefore, likely to be applicable to patients who have undergone cardiac surgery.

A retrospective observational multicentre study in 203 patients who required RRT after cardiac surgery, showed that late initiation of RRT (≥3 days after cardiac surgery) was associated with increased in-hospital mortality, worsening renal function and prolonged hospital stay, compared with early initiation of RRT (<3 days after cardiac surgery)[125]. However, owing to the limited number of studies addressing the timing of RRT initiation, the impact of early initiation of RRT on CSA-AKI outcome remains uncertain.

Intensity of RRT. Over the last decade, two large multicentre RCTs (the RENAL and ATN trials) have assessed the effect of different intensities of dialysis in critically ill patients with severe AKI[126,127]. Both studies demonstrated no difference in all-cause mortality between patients receiving higher intensity and standard intensity dialysis. Furthermore, an individual patient data meta-analysis of previous RCTs of RRT intensity in AKI (the IMPROVE-AKI study) confirmed that there was no survival difference between groups receiving different intensities of dialysis[128]. To date, no RCTs assessing RRT intensity have focused solely on patients who have undergone cardiac surgery.

Modalities of RRT. Different modalities of RRT have been used in severe AKI, including continuous RRT (CRRT), intermittent haemodialysis (IHD) and extended daily dialysis (EDD). CRRT is often used in haemodynamically unstable patients to control fluid and acid–base status, electrolyte disturbances and uraemia, as this modality provides continuous slower blood flow than does IHD. The KDIGO guidelines suggest the use of CRRT in haemodynamically unstable patients (Grade 2B recommendation)[122], although EDD may also be suitable for treatment in this setting[129]. EDD has the advantage of a lower cost than CRRT, together with providing haemodynamic tolerability[130].

Current RCTs and meta-analyses of general ICU populations suggest that survival and recovery of renal function are similar for both CRRT and IHD. The HaemoDiafe Study is a multicentre study of 360 patients with AKI and multiorgan dysfunction syndrome who were randomly assigned to receive IHD or continuous venovenous haemodiafiltration (CVVHDF)[131]. No difference in survival at 60 days was seen between these two groups. Similarly, in a pooled analysis of RCTs, recovery of kidney function seemed to be comparable between CRRT and IHD[132].

A randomized trial that compared EDD to CVVHDF in 80 patients with CSA-AKI found no marked difference in renal function, mortality, renal recovery and hospital stay between these two groups[133]. The cost of RRT was, however, markedly lower in the EDD group. Haemodynamic measurements, including heart rate and systolic and diastolic arterial blood pressures, were comparable in both groups. In summary, in the absence of RCTs addressing dialysis modality in patients undergoing cardiac surgery, the choice of RRT modality is likely to be based on patient characteristics and local expertise.

Duration of RRT. The optimal duration of RRT in the setting of cardiac surgery also remains unclear. A prospective observational study assessed CVVHDF for the treatment of cardiogenic shock along with acute renal failure after cardiac surgery. This study found that a CVVHDF duration of <50 h over 72 h was associated with a higher mortality risk compared with CVVHDF of >50 hours[134]. The indications for discontinuation of RRT according to KDIGO guidelines are when RRT is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs, or because RRT is no longer consistent with the goals of care[122]. In the absence of RCTs, the choice of RRT duration is likely to be based on clinical judgement.

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Patient and renal prognosis. The presence of CSA-AKI is associated with poor patient and renal prognosis (FIG. 2). Mortality following severe AKI that required RRT in the ICU setting was 52.6% at 60 days in the ATN study[126] and 44.7% at 90 days in the RENAL study[127]. A retrospective study showed that 30-day mortality in patients with CSA-AKI was 58.6%[135]. Positive fluid balance during the first day of RRT, poor cardiac function and high sequential organ failure assessment score were independent risk factors for 30-day mortality. Fluid balance to avoid fluid overload, therefore, seems to be more closely associated with short-term prognosis of patients with CSA-AKI receiving RRT, than are ultrafiltration volume and rate.

In the ATN study[126], which included patients undergoing cardiac surgery, complete recovery of kidney function (defined as serum creatinine level ≤0.5 mg/dl (44 µmol/l) above the baseline value) by 28 days after randomization was seen in 16.9% of patients. Partial recovery (defined as a serum creatinine level that remained at >0.5 mg/dl above baseline in patients who were not dependent on dialysis) was seen in 8.9% of patients. In the RENAL study[127], which also included patients undergoing cardiac surgery, 13.3% of patients were dependent on RRT at 28 days and 5.6% at 90 days after randomization. However, no specific data on renal recovery for patients undergoing cardiac surgery were provided in the RENAL trial.

The long-term consequences of CSA-AKI have been investigated in a systematic review of nine observational studies in 35,021 patients[136]. The occurrence of postoperative AKI was associated with a significantly increased risk of long-term mortality (HR 1.68, 95% CI 1.45–1.95). Patients with persistent renal dysfunction had higher long-term mortality risk (HR 2.71, 95% CI 1.26–5.82) than those who experienced recovery of renal function to baseline levels before hospital discharge.

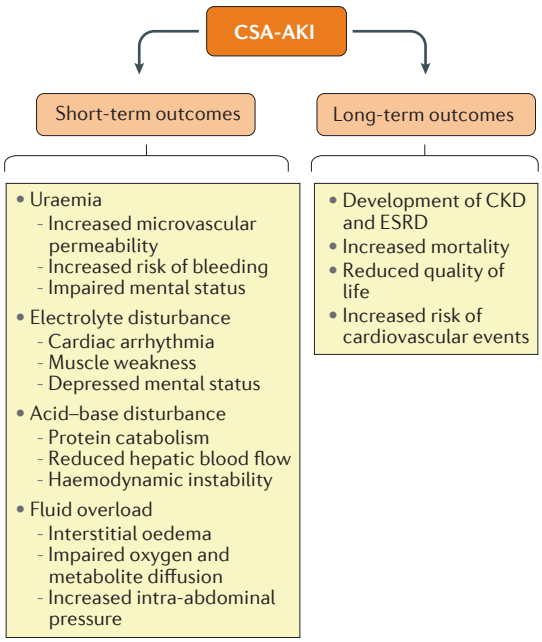

Figure 2 | **The effects of AKI on overall patient outcomes.** Cardiac surgery-associated acute kidney injury (CSA-AKI) can have short-term (occurring within 90 days of surgery) or long-term outcomes. Examples of these outcomes and of the clinical consequences or manifestations of short-term outcomes are illustrated. CKD, chronic kidney disease; ESRD, end-stage renal disease.

CSA-AKI in children

AKI is common in children after congenital cardiac surgery with CPB, with the reported incidence ranging from 28% to 51%[137,138], or up to 64% in neonates[139]. The TRIBE-AKI prospective multicentre cohort study, which included 131 children aged 1–18 years, demonstrated that CKD and hypertension are common 5 years following cardiac surgery, independent of postoperative AKI[140]. In children, the incidence of severe AKI requiring CRRT after cardiac surgery ranges from 1% to 17%[141,142], and severe AKI is associated with increased mortality[141]. In a prospective observational cohort study of 1,650 children undergoing cardiac surgery, 4.9% required CRRT[143]. Compared with other clinically ill paediatric patients receiving CRRT without cardiac surgery, cardiac surgery was associated with a prolonged duration of CRRT requirement for more than 14 days, and with increased mortality.

Younger age, longer CPB time, lower preoperative serum haemoglobin level[144], lower body weight and body surface area, and preoperative use of mechanical ventilation[145] are all associated with an increased risk of AKI after cardiac surgery in children. The biomarkers used for early detection of AKI after cardiac surgery in children differ, to some extent, from those used in adults. The use of NGAL as a biomarker in children has been extensively investigated. The diagnostic value of NGAL seems to be high in the paediatric setting, although a lack of consensus exists on the reference values in healthy children[146]. An elevation of serum or urine NGAL can be seen as early as 2 h after cardiac surgery[147]. Patients with elevated NGAL but with a normal serum creatinine level (in other words, subclinical AKI) have a 2–3-fold increase in risk of mortality or likelihood of requiring dialysis, compared with those with a normal NGAL level[148]. In addition, early detection of serum cystatin C (within 6 h of initiating CPB) is also a predictive factor for the development of AKI in paediatric patients undergoing cardiac surgery[149]. Postoperative serum levels of brain natriuretic peptide, however, did not predict AKI after cardiac surgery in a multicentre, prospective cohort study of 121 children under 2 years of age. An increase in the serum level of brain natriuretic peptide was, however, associated with prolonged hospital stay and a greater requirement for mechanical ventilation[150]. Similarly to adult patients with CSA-AKI, the use of IL-18, L-FABP, KIM1, TIMP2 and IGFBP7, alone or in combination, enables early detection of AKI in paediatric patients. However, the small sample size and heterogeneity in the definition of AKI that was used in these studies suggest the need for future large studies to confirm the validity and applicability of using biomarkers in paediatric CSA-AKI.

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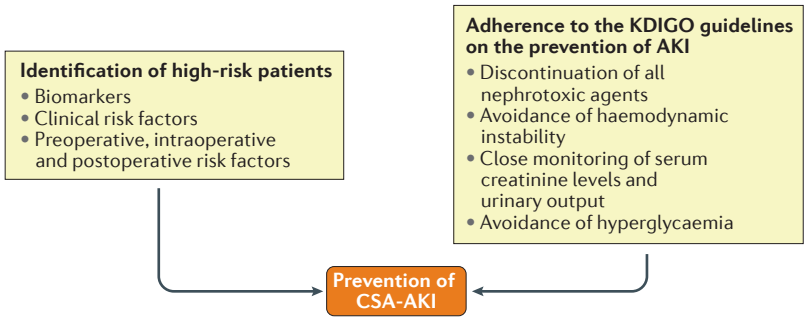
Identification of high-risk patients
• Biomarkers
• Clinical risk factors
• Preoperative, intraoperative and postoperative risk factors
Adherence to the KDIGO guidelines on the prevention of AKI
• Discontinuation of all nephrotoxic agents
• Avoidance of haemodynamic instability
• Close monitoring of serum creatinine levels and urinary output
• Avoidance of hyperglycaemia
Prevention of CSA-AKI

Figure 3 | **Preventive strategies for CSA-AKI.** The prevention of cardiac surgery-associated acute kidney injury (CSA-AKI) relies on the identification of high-risk patients using three strategies: analysis of biomarkers, assessment of clinical risk factors and identification of preoperative, intraoperative and postoperative risk factors. In addition, adherence to the Kidney Disease: Improving Global Outcomes (KDIGO) treatment guidelines[10] might reduce the risk of AKI.

The pathogenesis of CSA-AKI in children seems to be similar to that in adults[151]. Fluid overload owing to a reduction in GFR seems to be a particularly important independent prognostic factor for morbidity and mortality in children with AKI[151]. A number of pharmacological interventions (including furosemide, aminophylline and fenoldopam) to improve renal outcomes have been tested, with variable results[152,153]. Aminophylline is an adenosine receptor antagonist that has a renoprotective effect via dilatation of the renal vasculature in ischaemic AKI models[154]. A retrospective cohort study demonstrated that in children undergoing cardiac surgery, intraoperative use of aminophylline was superior to furosemide in reversing oliguria in the early postoperative period[155]. However, a double-blind, randomized, placebo-controlled trial that assessed postoperative use of aminophylline in 144 children after congenital heart surgery with CPB, found that aminophylline did not have a marked effect on the prevention of CSA-AKI compared with placebo[156].

The role of diuretics in paediatric CSA-AKI remains controversial, and their use has resulted in increased mortality in some studies[157,158]. As pharmacological agents seem to be less effective in children than in adults in the prevention and treatment of fluid overload in AKI after cardiac surgery, early use of RRT has been increasingly assessed in the paediatric setting.

In contrast to adult patients with severe AKI who commonly receive haemodialysis, peritoneal dialysis is one of the most common RRT modalities used in children with AKI following cardiac surgery. Some studies suggested that early commencement of peritoneal dialysis before marked fluid overload in children can reduce mortality after cardiac surgery[159]. Peritoneal dialysis might also benefit paediatric patients with fluid overload by providing improved nutrition and by reducing the levels of inflammatory cytokines[160]. A RCT in 73 infants undergoing cardiac surgery showed that in comparsion to postoperative furosemide for the management of fluid overload, early use of peritoneal dialysis was associated with less fluid overload, shorter duration of requirement for mechanical ventilation and less electrolyte imbalance[161].

Practical challenges and future trials

CSA-AKI is a complex and dynamic syndrome for which clinical trials are difficult to conduct. Thus, management of CSA-AKI remains a major practical challenge for intensivists, nephrologists, surgeons and anaesthetists. Sufficient preventive and therapeutic strategies for the management of CSA-AKI and adequate animal models are lacking. However, preliminary evidence suggests that avoidance of nephrotoxins and haemodynamic instability, and careful control of hyperglycaemia, might help to alleviate the risk of AKI. Control of hyperglycaemia might be further facilitated by new technologies for the continuous and semi-continuous measurement of glucose in the ICU[162,163]. These measures are almost cost-free and can be implemented in day-to-day clinical practice (FIG. 3).

In addition to avoiding iatrogenic injury, a need exists to conduct trials in areas of CSA-AKI management that might be improved to enable better renal outcomes. For example, increasing oxygen delivery by regulating pump flow and haematocrit during CBP might reduce AKI incidence[164]. Maintaining an intraoperative mean arterial pressure (MAP) of >65 mmHg might also reduce the incidence of postoperative AKI[165]. In patients with postoperative vasoplegic syndrome, AKI might be prevented with the use of low-dose vasopressin[166]. Avoidance of a low cardiac index (<2 l/min/m^2) in the first 48 hours after cardiac surgery may also be protective[167]. Furthermore, only scant data exists on optimal fluid management after cardiac surgery. Whether avoidance of a strongly positive fluid balance (>2 l over the first 24 h) can attenuate AKI remains an important clinical question. Trials to address these challenges have physiological plausibility and are a priority in the field of CSA-AKI management. Finally, the use of biomarkers for the early detection of AKI after cardiac surgery and for monitoring disease progression urgently needs to be further explored to reduce the burden of AKI. Although a number of serum and urine biomarkers have been investigated over the last decades, no 'ideal' biomarker is available that is superior to traditional diagnostic methods for AKI. Trials assessing the clinical applicability of combined use of biomarkers and clinical evaluation of AKI after cardiac surgery are worth considering.

Future trials in patients undergoing cardiac surgery are likely to focus on gaining data that facilitates improvements in three key areas: blood pressure and overall haemodynamic support, the technology and monitoring of renal protection during CPB, and the early detection of renal stress. Several pilot phase I and phase II trials of such approaches are likely to be reported in the next few years. However, given the heterogeneity of patients, surgical modalities, risk factors and pathophysiological mechanisms, improvements will probably be slow and incremental.

The translation of current evidence into clinical practice, especially in the areas of early detection, novel biomarkers, definitions and avoidance of aggravating factors, continues to be hindered by the fragmentation and complexity of care that affects patients with CSA-AKI worldwide — cardiac surgeons, perfusionists, anaesthesiologists, intensivists and nephrologists are all involved

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in the management of this condition. The possibility exists, however, that with improved means of electronic communication, clinical decision support systems can be developed and tested to provide reminders to clinicians to avoid nephrotoxins, fluid overload, hypotension and low cardiac output states in patients with CSA-AKI.

Conclusions

AKI is a common and important complication of cardiac surgery and is associated with increased short-term and long-term mortality and morbidity. Early identification of high-risk patients, early diagnosis of AKI and the development of clinical strategies that stress prevention, avoidance of nephrotoxins, a focus on the optimization of systemic haemodynamics and the avoidance of both fluid depletion and fluid overload, remain the mainstay of the current clinical management of CSA-AKI. Given the magnitude of the problem, further large clinical trials assessing potential pharmacological agents and non-pharmacological therapies for the prevention and treatment of CSA-AKI remain a priority in the fields of nephrology and intensive care medicine[44].

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